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IMPROVED DRUG DELIVERY SYSTEM

The present invention relates to an improved drug delivery system and, in particular, to an improved drug delivery system for the oral administration of lipophilic poorly water-soluble drugs in immediate release dosage forms.

The bioavailability of lipophilic, poorly water-soluble drugs when administered orally in solid dosage forms (such as tablets) is notoriously low and variable. This has led to the development of dosage forms in which the drug is pre-dissolved in either a lipid vehicle or a mixture of a lipid vehicle and a surfactant or a ternary mixture of a lipid vehicle, a surfactant and a co-solvent. Such compositions provide an increased bioavailability of the drug but only at the cost of increased complexity and, in most cases, the need to include very high levels (30% or greater) of surfactant or emulsifier.

Existing lipid-based delivery vehicles for lipophilic drugs include the simple solution of the drug in a lipophilic vehicle, self-emulsifying oil systems, micro-emulsions and liposomes. The properties and application characteristics of lipophilic drug delivery vehicles have been the subject of numerous reviews - for example, Humberstone & Charman (1997) Advanced Drug Delivery Review v.25, 103-128 and O'Driscoll (2002) European Journal of Pharmaceutical Science v.15, 405-415.

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Lipophilic Solution.

A number of drugs have an appreciable solubility in lipophilic oils (especially triacyl glycerides) alone. It is therefore possible to administer the drug as a simple solution in a capsule and obtain satisfactory absorption and bioavailability. However, the dispersion kinetics of such a formulation cannot be expected to be as rapid as would be observed for a pre-dispersed system. The slow dispersion of the formulation is a major limitation of this dosage form.

Self-emulsifying Oil Systems

These are sometimes referred to as SEDDS ('self-emulsifying drug delivery systems') and comprise a mixture of an oil and a surfactant that spontaneously forms an oil-in-water emulsion when diluted with water. The solubility of the drug is typically enhanced by the presence of the surfactant - which is usually present in concentrations as high as or greater than 30%. Co-solvents such as ethanol, propylene glycol and polyethylene glycol are sometimes added in order to increase the solubility of the drug. This dosage form is a lipophilic, isotropic liquid which may be filled into capsules and which, when liberated from the capsule in the gastrointestinal tract, forms a dispersion of small drug-containing oil/surfactant droplets which spread rapidly. The main disadvantage of SEDDS relates to the presence of the large amounts of surfactant, which, apart from potentially having a harmful effect on the intestinal wall, adds to the cost and complexity of the formulation. Examples of such compositions are disclosed in US Patents Nos. 6436430 and 6284268.

Microemulsion preconcentrates

These are essentially similar to SEDDS and comprise isotropic mixtures of drug, lipid, surfactant and (if required) co-solvent and co-surfactant. As with the self-emulsifying drug delivery systems, on addition to an aqueous medium these systems disperse to form liquid/liquid dispersions. The primary difference between microemulsion preconcentrates and SEDDS is the nature of the dispersion formed, where the microemulsion preconcentrates disperse to form thermodynamically stable microemulsions. Microemulsions have been shown to enhance the bioavailability of lipophilic drugs but suffer from the same major disadvantage as for SEDDS - the very high level of surfactant needed for their formation. Examples of such compositions are disclosed in US Patents Nos. 5993858 and 6309665.

Liposomes

Liposomes consist of ordered layers of phospholipid molecules which encapsulate a central aqueous lumen. The possibility exists for lipophilic drugs to be solublised within the phospholipid layers. The drug carrying capabilities of liposomes are sufficient for use in parenteral formulations, but are not particularly suitable for use in oral dosage forms. Furthermore, liposomes are unstable and expensive to produce and therefore have limited potential for the delivery of lipophilic drugs. Examples of such compositions are disclosed in US Patents Nos. 4746516 and 6090407.

Other dosage forms include the conversion of microemulsions into solid or semisolid nano particles and

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the use of polyaphrons. US Patent No. 4999198 discloses a polyaphron comprising a continuous phase and a disperse phase in which a drug, specifically scopolamine, is carried. The patent describes the slow release of the drug from the polyaphron into a medium with which the polyaphron is in contact and in particular the transdermal delivery of drugs. The invention described here is different from that previously described in US Patent No. 4999198. No reference has previously been given to the use of such polyaphrons as an oral delivery system which is compatible with hard or soft gelatin capsules. No specific water to lipid phase ratio is given in the previous patent. Furthermore, scopolamine is the only drug specifically mentioned.

The disadvantages of the oral formulations for the delivery of lipophilic poorly water-soluble drugs have been discussed above. None of the current formulations is particularly satisfactory.

We have now developed a readily dispersible two-phase system for the oral delivery of poorly water-soluble drugs which has a low water content (less than 10% w/w water) and therefore gives the system a good compatibility with gelatin, thereby enabling the drug formulation to be encapsulated in hard or soft gelatin capsules. Furthermore, the two-phase system is simple to produce and requires the use of only a limited amount of potentially expensive and harmful surfactants.

Accordingly, the present invention provides an oral drug delivery system which comprises a biliquid foam comprising

from 1 to 20% by weight of a continuous hydrophilic phase,

from 70 to 98% by weight of a pharmaceutically acceptable oil which forms a discontinuous phase, the said pharmaceutically acceptable oil having dissolved or dispersed therein a poorly water-soluble drug in an amount of from 0.1 to 20% by weight

and the biliquid foam including therein from 0.5 to 10%, preferably 0.5 to 5%, by weight of a surfactant to enable the formation of a stable biliquid foam, all percentages being based upon the total weight of the formulation.

By the term "biliquid foam" which is used herein, which is also referred to in the art as a "polyaphron", is meant a non-isotropic dispersion of a non-polar liquid suspended in a continuous polar phase.

By the term "poorly water-soluble drug" as used herein is meant a drug which will dissolve in water in an amount of less than 1% by weight. The discontinuous phase contains the drug in an amount of 0.1 to 20% by weight, for example 1 to 10% by weight or 2 to 7% by weight. It is also possible for some drug to be present in the continuous hydrophilic phase, particularly if a cosolvent such as a polyethylene glycol is used.

The pharmaceutically acceptable oil which is used in the present invention is preferably a mono-, di- or triglyceride, or a mixture thereof. In particular the mono-, di- or triglycerides are preferably the glycerol esters of fatty acids containing from 6 to 22 carbon atoms.

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Examples of oils which may be used in the present invention include almond oil, babassu oil, blackcurrant seed oil, borage oil, canola oil, castor oil, coconut oil, cod liver oil, corn oil, cottonseed oil, evening primrose oil, fish oil, grapeseed oil, mustard seed oil, olive oil, palm kernel oil, palm oil, peanut oil, rapeseed oil, safflower oil, sesame oil, shark liver oil, soybean oil, sunflower oil, walnut oil, wheat germ oil, hydrogenated castor oil, hydrogenated coconut oil, hydrogenated cottonseed oil, hydrogenated palm oil, hydrogenated soybean oil, partially hydrogenated soybean oil, hydrogenated vegetable oil, modified triglycerides, caprylic/capric glycerides, fractionated triglycerides, glyceryl tricaprate, glyceryl tricaproate, glyceryl tricaprylate, glyceryl tricaprylate/caprate, glyceryl tricaprylate/caprate, glyceryl tricaprylate/caprate/laurate, glyceryl tricaprylate/caprate/linoleate, glyceryl tricaprylate/caprate/stearate, glyceryl trilaurate, glyceryl trilinoleate, glyceryl trilinolenate, glyceryl trioleate, glyceryl triundecanoate, linoleic glycerides, saturated polyglycolized glycerides, synthetic medium chain triglyceride containing primarily C_8-C_{12} fatty acid chains, medium chain triglycerides, long chain triglycerides, modified triglycerides, fractionated triglycerides, and mixtures thereof.

Examples of mono and diglycerides which may be used in the present invention include propylene glycol mono and diesters having from 15 to 40 carbon atoms, including hydrolysed coconut oils (e.g. Capmul MCM), hydrolysed corn oil (e.g. Maisine 35-1).

The monoglycerides and diglycerides are mono- or di-saturated fatty acid esters of glycerol having eight to sixteen carbon chain length.

Essential oils may also be used in the present invention.

The surfactant used in the present invention may be incorporated into either or both phases of the biliquid foam. The surfactant used in the present invention is preferably an alkyl polyglycol ether, an alkyl polyglycol ester, an ethoxylated alcohol, a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene fatty acid ester, an ionic or non-ionic surfactant, a hydrogenated castor oil/polyoxyethylene glycol adducts containing from 25 to 60 ethoxy groups a castor oil/polyoxyethylene glycol adduct containing from 25 to 45 ethoxy groups, a sorbitan fatty acid ester (for example Span 20 or Span 80), a block copolymer of ethylene oxide and propylene oxide (for example Pluronic L121 or Pluronic F68), or a mixture thereof. The surfactant may be used in an amount of from 0.5 to 10% by weight of the biliquid foam but preferably is used in an amount of from 0.5 to 5%, even more preferably 1 to 2%, by weight of the biliquid foam.

A co-emulsifier may be used in the formation of the biliquid foams in an amount sufficient to complete the solubilization of the poorly water-soluble drug. A suitable co-emulsifier is a phosphoglyceride, a phospholipid, for example lecithin, or a free fatty acid that is liquid at room temperature, for example iso-stearic acid, oleic acid, linoelic acid or linolenic acid.

The continuous hydrophilic phase of the biliquid foam may comprise water or may comprise an aqueous phase which includes therein an additional component to reduce the affinity of the aqueous phase for a capsule forming material such as gelatin. The additional component may be a salt such as sodium chloride, or a co-solvent such as an aliphatic alcohol, polyethylene glycol, propylene glycol or glycerol, or mixtures thereof, or a gelling agent such as alginate gums or their salts, guar gum, locust bean gum, xanthan gum, gum acacia, gelatin, hydroxymethyl-cellulose hydroxyethylcellulose, hydroxypropyl-cellulose, carboxymethylcellulose or its salts, bentonites, magnesium aluminium silicates, "Carbomers" (salts of cross-linked polymers of acrylic acid), or glyceryl polymethacrylates or their dispersions in glycols, or a polyvinylpyrrolidone polymer or a water-dispersible copolymer thereof, or any appropriate mixture of any of these polymers and gums.

Alternatively, the hydrophilic phase may be non-aqueous and may be, for example, an aliphatic alcohol, polyethylene glycol, propylene glycol or glycerol, or mixtures thereof.

Water-soluble inorganic salts may be added to improve the stability of the biliquid foams, such as those formed from monovalent cations such as Na^+, K^+ or NH_4^+, divalent cations such as Ca^{++} or Mg^{++} or trivalent cations such as Al^{+++}. Water soluble polysaccharides such as sucrose, glucose or fructose may also be added to improve stability.

Poorly water-soluble drugs which may be used in the present invention include the following:

Analgesics and anti-inflammatory agents: aloxiprin, auranofin, azapropazone, benorylate, diflunisal, etodolac, fenbufen, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac.

Anthelmintics: albendazole, bephenium hydroxynaphthoate, cambendazole, dichlorophen, ivermectin, mebendazole, oxamniquine, oxfendazole, oxantel embonate, praziquantel, pyrantel embonate, thiabendazole.

Anti-arrhythmic agents: amiodarone HCl, disopyramide, flecainide acetate, quinidine sulphate. Anti-bacterial agents: benethamine penicillin, cinoxacin, ciprofloxacin HCl, clarithromycin, clofazimine, cloxacillin, demeclocycline, doxycycline, erythromycin, ethionamide, imipenem, nalidixic acid, nitrofurantoin, rifampicin, spiramycin, sulphabenzamide, sulphadoxine, sulphamerazine, sulphacetamide, sulphadiazine, sulphafurazole, sulphamethoxazole, sulphapyridine, tetracycline, trimethoprim.

Anti-coagulants: dicoumarol, dipyridamole, nicoumalone, phenindione.

Anti-depressants: amoxapine, maprotiline HCl, mianserin HCl, nortriptyline HCl, trazodone HCl, trimipramine maleate.

Anti-diabetics: acetohexamide, chlorpropamide, glibenclamide, gliclazide, glipizide, tolazamide, tolbutamide.

Anti-epileptics: beclamide, carbamazepine, clonazepam, ethotoin, methoin, methsuximide, methylphenobarbitone, oxcarbazepine, paramethadione, phenacemide, phenobarbitone, phenytoin, phensuximide, primidone, sulthiame, valproic acid.

Anti-fungal agents: amphotericin, butoconazole nitrate, clotrimazole, econazole nitrate, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, miconazole, natamycin, nystatin, sulconazole nitrate, terbinafine HCl, terconazole, tioconazole, undecenoic acid.

Anti-gout agents: allopurinol, probenecid, sulphinpyrazone.

Anti-hypertensive agents: amlodipine, benidipine, darodipine, dilitazem HCl, diazoxide, felodipine, guanabenz acetate, isradipine, minoxidil, nicardipine HCl, nifedipine, nimodipine, phenoxybenzamine HCl, prazosin HCl, reserpine, terazosin HCl.

Anti-malarials: amodiaquine, chloroquine, chlorproguanil HCl, halofantrine HCl, mefloquine HCl, proguanil HCl, pyrimethamine, quinine sulphate.

Anti-migraine agents: dihydroergotamine mesylate, ergotamine tartrate, methysergide maleate, pizotifen maleate, sumatriptan succinate.

Anti-muscarinic agents: atropine, benzhexol HCl, biperiden, ethopropazine HCl, hyoscyamine, mepenzolate bromide, oxyphencylcimine HCl, tropicamide.

Anti-neoplastic agents and Immunosuppressants: aminoglutethimide, amsacrine, azathioprine, busulphan, chlorambucil, cyclosporin, dacarbazine, estramustine, etoposide, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, mitozantrone, procarbazine HCl, tamoxifen citrate, testolactone.

Anti-protazoal agents: benznidazole, clioquinol, decoquinate, diiodohydroxyquinoline, diloxanide furoate, dinitolmide, furzolidone, metronidazole, nimorazole, nitrofurazone, ornidazole, tinidazole.

Anti-thyroid agents: carbimazole, propylthiouracil.

Anxiolytic, sedatives, hypnotics and neuroleptics: alprazolam, amylobarbitone, barbitone, bentazepam, bromazepam, bromperidol, brotizolam, butobarbitone, carbromal, chlordiazepoxide, chlormethiazole, chlorpromazine, clobazam, clotiazepam, clozapine, diazepam, droperidol, ethinamate, flunanisone, flunitrazepam, fluopromazine, flupenthixol decanoate, fluphenazine decanoate, flurazepam, haloperidol, lorazepam, lormetazepam, medazepam, meprobamate, methaqualone, midazolam, nitrazepam, oxazepam, pentobarbitone, perphenazine pimozide, prochlorperazine, sulpiride, temazepam, thioridazine, triazolam, zopiclone.

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β-Blockers: acebutolol, alprenolol, atenolol, labetalol, metoprolol, nadolol, oxprenolol, pindolol, propranolol.

Cardiac Inotropic agents: amrinone, digitoxin, digoxin, enoximone, lanatoside C, medigoxin.

Corticosteroids: beclomethasone, betamethasone, budesonide, cortisone acetate, desoxymethasone, dexamethasone, fludrocortisone acetate, flunisolide, flucortolone, fluticasone propionate, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone.

Diuretics: acetazolamide, amiloride, bendrofluazide, bumetanide, chlorothiazide, chlorthalidone, ethacrynic acid, frusemide, metolazone, spironolactone, triamterene.

Anti-parkinsonian agents: bromocriptine mesylate, lysuride maleate.

Gastro-intestinal agents: bisacodyl, cimetidine, cisapride, diphenoxylate HCl, domperidone, famotidine, loperamide, mesalazine, nizatidine, omeprazole, ondansetron HCl, ranitidine HCl, sulphasalazine.

Histamine H_1-Receptor Antagonists: acrivastine, astemizole, cinnarizine, cyclizine, cyproheptadine HCl, dimenhydrinate, flunarizine HCl, loratadine, meclozine HCl, oxatomide, terfenadine.

Lipid regulating agents: bezafibrate, clofibrate, fenofibrate, gemfibrozil, probucol.

Nitrates and other anti-anginal agents: amyl nitrate, glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate, pentaerythritol tetranitrate.

Nutritional agents: betacarotene, vitamin A, vitamin B2, vitamin D, vitamin E, vitamin K.

Opioid analgesics: codeine, dextropropyoxyphene, diamorphine, dihydrocodeine, meptazinol, methadone, morphine, nalbuphine, pentazocine.

Sex hormones: clomiphene citrate, danazol, ethinyl estradiol, medroxyprogesterone acetate, mestranol, methyltestosterone, norethisterone, norgestrel, estradiol, conjugated oestrogens, progesterone, stanozolol, stibestrol, testosterone, tibolone.

Stimulants: amphetamine, dexamphetamine, dexfenfluramine, fenfluramine, mazindol.

Pharmaceutically acceptable salts, isomers and derivatives thereof may be substituted for these drugs. Mixtures of lipophilic drugs may be used where therapeutically effective.

The discontinuous phase of the present invention comprises 70 to 98% by weight, preferably from 80 to 96% by weight, more preferably from 90 to 95% by weight of the biliquid foam. The continuous hydrophilic phase comprises from 1 to 20% by weight, preferably from 2 to 10% by weight of the biliquid foam.

The oral drug delivery systems of the present invention are preferably presented in a unit dosage form. The preferred unit dosage form comprises capsules filled with the biliquid foam, for example hard or soft gelatin capsules. The use of the gelatin capsules is made possible by the low water content of the biliquid foam which ensures good compatibility both with the hard and soft gelatin capsules and the optional incorporation into the aqueous phase of an additional component which reduces the affinity of the aqueous phase for the capsule material. This is an advantage over the currently available lipid dispersions and provides a better bioavailability of the drug as compared to tablets.

Each unit dosage form will comprise, for example, from 0.5mg to 1000mg, preferably 0.5 to 200mg of the drug, for example in up to a 1000mg, preferably 100mg, dosage form.

The biliquid foams of the drug delivery systems may also be presented as dilutable concentrates which are infinitely dilutable in a co-solvent such as water or a water compatible aliphatic alcohol, polyethylene glycol, propylene glycol or glycerol, or mixtures thereof. Dilution of the biliquid foam preparations is possible and they may be incorporated into a drink, syrup or linctus.

The biliquid foam compositions of the present invention may also contain other additives such as preservatives or antimicrobial agents(for instance to prevent microbiological spoilage). These additives may be included in the non-polar liquid or the continuous phase.

It will be understood that the inclusion of these additives will be at the levels and with the type of materials which are found to be effective and useful. Care needs to be taken in the choice and amount of these additives to prevent compromise to the other performance advantages of the present invention.

Methods of producing biliquid foams are described in US-A-4486333 involving the preliminary formation of a gas foam in order to provide a sufficiently large surface area on which the biliquid foam can subsequently be formed. It has been found that the prior formation of a gas foam is not required to manufacture a stable biliquid foam, provided that a suitable stirring mechanism is provided in the manufacturing vessel.

Such an apparatus comprises a tank provided with a stirrer in which the stirrer blade breaks the interface between the liquid and air. A delivery device is provided through which the oil phase (non-polar liquid), which will comprise the internal phase of the dispersion is delivered to the tank. The design of the delivery device is such that the rate of addition of the internal phase fluid can be controlled and varied during the production process. A feature of the production process is that the internal (oil) phase is added to the stirred aqueous phase slowly at first until sufficient droplets have been formed to constitute a large surface area for the more rapid formation of new droplets. At this point, the rate of addition of the oil phase may be increased.

The production process consists of the following steps:

1. The addition of one or more chosen surfactants to one or other or both phases (as previously determined by experiment).

2. The charging of the aqueous phase into the bottom of a process vessel.

3. The incorporation of the stirrer into the vessel so that it stirs the surface of the aqueous phase.

4. Adjustment of the stirrer speed to a previously determined level.

5. The slow addition of the internal (oil) phase containing the poorly water-soluble drug dissolved or dispersed therein whilst continuing to stir at the prescribed speed.

6. The speeding up of the rate of addition of the oil phase once a prescribed amount (usually between 5% and 10% of the total amount to be added) has been added.

The stirring rate and the rate of addition of the oil phase are variables, the values of which depend upon the detailed design of the manufacturing plant (in particular, the ratio of tank diameter to impeller diameter), the physico-chemical properties of the oil phase and the nature and concentrations of the chosen surfactants. These can all be pre-determined by laboratory or pilot plant experiment.

It will be understood by those skilled in the art that other manufacturing methods may be used, as appropriate.

Although the stability of the biliquid foams is generally good, they may be stabilised by the addition of an aqueous gel and, accordingly, the present invention includes within its scope a stable dispersion which comprises from 1

to 80% by weight of a biliquid foam and from 20 to 99% by weight of an aqueous gel.

The aqueous gel will preferably be formed from a colloidal polymer or gum suspended in water, at a concentration of from 0.05 to 20% by weight, more preferably from 0.2 to 1% by weight. Suitable polymers or gums are, for example, alginate gums or their salts, guar gum, locust bean gum, xanthan gum, gum acacia, gelatin, hydroxymethylcellulose hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose or its salts, bentonites, magnesium aluminium silicates, "Carbomers" (salts of cross-linked polymers of acrylic acid), or glyceryl polymethacrylates or their dispersions in glycols, or any appropriate mixture of any of these polymers and gums.

The present invention will be further described with reference to the following examples:

Biliquid Foam Preparation

A suitable vessel was charged with the aqueous phase of the biliquid foam. The drug was dissolved in the oil phase. The oil phase containing the drug was then added at a constant rate with stirring, using a sweep stirrer or an orbital mixer. After completion of the oil addition, the stirring was continued until the size of the oil droplets became stable or reached a desired size.

Example 1

	%	Weight(g)
Oil phase		
Caprylic/capric triglyceride	90	27
Halofantrine	5	1.5
Aqueous phase		
Castor oil/polyoxyethylene glycol (35) adduct	1	0.3
Deionised water	4	1.2
Total	100	30.0

Example 2

	%	Weight(g)
Oil phase		
Caprylic/capric triglyceride	90	27
Halofantrine	5	1.5
Aqueous phase		
Hydrogenated castor oil/polyoxyethylene glycol (40) adduct	1	0.3
Deionised water	4	1.2
Total	100	30.0

Example 3

	%	Weight(g)
Oil phase		
Caprylic/capric triglyceride	90	27
Halofantrine	5	1.5
Aqueous phase		
Hydrogenated	1	0.3

castor oil/polyoxyethylene glycol (60) adduct		
Deionised water	4	1.2
Total	100	30.0

Example 4

Oil phase	**%**	**Weight(g)**
Soybean oil BP	90	27
Halofantrine	5	1.5
Aqueous phase		
Hydrogenated castor oil/polyoxyethylene glycol (35) adduct	1	0.3
Deionised water	4	1.2
Total	100	30.0

Example 5

Oil Phase	**%**	**Weight (g)**
Caprylic/capric triglycerides	90	27
Cyclosporin	5	1.5
Aqueous Phase		
Hydrogenated castor oil/ polyoxyethylene glycol (60) adduct	1	0.3
Deionised water	4	1.2
Total	100	30.0

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Example 6

Oil Phase	%	Weight (g)
Caprylic/capric triglycerides	40	12
Glyceryl monolinoleate (Maisine 35)	40	12
Cyclosporin	10	3.0
Aqueous Phase		
Hydrogenated castor oil/ polyoxyethylene glycol (60) adduct	1	0.3
1% aqueous calcium chloride solution	9	2.7
Total	100	30..0

Example 7

Oil Phase	%	Weight (g)
Soybean Oil BP	85.5	25.65
Halofantrine	4.5	1.35
Aqueous Phase		
Castor oil/polyoxyethylene glycol (60) adduct	2	0.6
Sodium chloride	1	0.3
Deionised water	7	2.1
Total	100	30.0

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Example 8

The following formulation could be prepared:

Oil Phase	**%**	**Weight (g)**
Soybean Oil BP	75.2	22.56
Halofantrine	4	1.2
Oleic Acid	0.8	0.24
Aqueous Phase		
Ethanol (DEB 100)	14	4.2
Deionised water	5.6	1.68
Hydrogenated castor oil/ polyoxyethylene glycol (45) adduct	0.4	0.12
Total	100	30.0

Examples 9, 10, 11 and 12 show formulations containing high concentrations of propylene glycol as a co-solvent for poorly water-soluble drugs.

Example 9

The following formulation could be prepared:

Oil Phase	**%**	**Weight (g)**
Caprylic/capric triglycerides	85	25.5
Halofantrine	4	1.2
Hydrogenated castor oil/ polyoxyethylene glycol (40) adduct	1	0.3

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Aqueous Phase		
Propylene glycol	9.5	2.85
Deionised water	0.5	0.15
Total	100	30.0

Example 10

The following formulation could be prepared:

Oil Phase	**%**	**Weight (g)**
Caprylic/capric triglycerides	85	25.5
Halofantrine	4	1.2
Castor oil/polyoxyethylene glycol (35) adduct	1	0.3
Aqueous Phase		
Propylene glycol	9.5	2.85
Deionised water	0.5	0.15
Total	100	30.0

Example 11

The following formulation could be prepared:

Oil Phase	**%**	**Weight (g)**
Soybean Oil BP	84	25.2
Halofantrine	5	1.5
Castor oil/polyoxyethylene glycol (35) adduct	1	0.3

Aqueous Phase		
Propylene glycol	9	2.7
Deionised water	1	0.3
Total	100	30.0

Example 12

The following formulation could be prepared:

Oil Phase	**%**	**Weight (g)**
Soybean Oil BP	84	25.2
Halofantrine	5	1.5
Castor oil/polyoxyethylene glycol (40) adduct	1	0.3
Aqueous Phase		
Propylene glycol	9.5	2.85
Deionised water	0.5	0.15
Total	100	30.0

Example 13 illustrates the use of glycerine as a co-solvent (for poorly water-soluble drugs) in the continuous phase.

Example 13

The following formulation could be prepared:

Oil Phase	**%**	**Weight (g)**
Caprylic/capric triglycerides	84	25.2
Halofantrine	5	1.5
C12-13 Pareth-3	1	0.3

Aqueous Phase		
Glycerine BP	7	2.1
1% aqueous sodium laureth sulphate	3	0.9
Total	100	30.0

Examples 14 and 15 illustrate the use of polyethyleneglycols as co-solvents for poorly water-soluble drugs.

Example 14

The following formulation could be prepared:

Oil Phase	**%**	**Weight (g)**
Caprylic/capric triglycerides	84	25.2
Halofantrine	5	1.5
C12-13 Pareth-3	1	0.3
Aqueous Phase		
PEG-6	5	1.5
1% aqueous sodium laureth sulphate	5	1.5
Total	100	30.0

Example 15

The following formulation could be prepared:

Oil Phase	**%**	**Weight (g)**
Soybean Oil BP	84	25.2
Halofantrine	5	1.5
Castor oil/polyoxyethylene glycol (40) adduct	1	0.3

Aqueous Phase			
PEG-6		10	3
Total		100	30.0

Example 16

In order to demonstrate the advantages of the present invention a test was carried out to compare formulations of the present invention with a tablet.

A commercial formulation Halfan® (Batch no. 558, SmithKline & French, UK) was tested. Analysis showed that it contained 248 mg Halofantrine. The bioavailability was tested in fasted male beagle dogs and compared with that obtained using the formulation of Example 7 (LCT BLF) and the formulation of Example 7 except that the soybean oil is replaced with caprylic/capric triglycerides (MCT BLF). The dogs, weighing from 12 to 19 kg, were dosed in a randomised crossover study. The dogs were fasted for 21 hours prior to dosing. Blood samples were collected at -15 min (pre-close blank) and subsequently at 15, 30, 60 and 90 mins and at 2, 3, 4, 6, 8, 10, 24, 32, 48 and 72 hours post-dosing. The following results were obtained:

Parameter	Tablet	MCT BLF	LCT BLF
C_{max} (ng/ml)	85	176	781
t_{max} (h)	1.3	3.8	2.3
$AUC^{0-\infty}$(ng.ml/h)	1131	2800	7754
Relative bioavailability compared with tablet (%)	100	248	686

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C_{max} = concentration maximum measured in blood after oral administration.

T_{max} = time from administration taken to reach C_{max}.

AUC = Area under curve: a measure of the total amount appearing in the blood over time.

Relative bioavailability compared with tablets(%) = Relative bioavailability compared to that from the tablet, expressed as a percentage.